

# Association of Type D personality with increased vulnerability to depression: is there a role for inflammation or endothelial dysfunction? - the Maastricht Study

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## Research report

# Association of Type D personality with increased vulnerability to depression: Is there a role for inflammation or endothelial dysfunction? – The Maastricht Study



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## ABSTRACT

**Background:** Type D personality – the combination of negative affectivity (NA) and social inhibition (SI) – has been associated with depression but little is known about underlying mechanisms. We examined whether (1) Type D is a vulnerability factor for depression in general, (2) Type D is associated with inflammation or endothelial dysfunction, and (3) these biomarkers alter the possible association between Type D and depression.

**Methods:** In the Maastricht Study, 712 subjects underwent assessment of NA, SI and Type D personality (DS14), depressive disorder (Mini-International Neuropsychiatric Interview) and depressive symptoms (Patient Health Questionnaire-9). Plasma biomarkers of inflammation (hsCRP, SAA, sICAM-1, IL-6, IL-8, TNF- $\alpha$ ) and endothelial dysfunction (sVCAM-1, sICAM-1, E-selectin, vWF) were measured with sandwich immunoassays or ELISA and combined into standardized sumscores.

**Results:** Regarding personality, 49% of the study population was low in NA and SI, 22% had SI only, 12% NA only and 17% had Type D. Depressive disorder and depressive symptoms were significantly more prevalent in Type D versus the other three personality subgroups. Multivariable regression analyses showed that Type D was associated with inflammation ( $\beta=0.228$ ,  $p=0.014$ ) and endothelial dysfunction ( $\beta=0.216$ ,  $p=0.022$ ). After adjustment for these biomarkers, Type D remained independently associated with increased vulnerability to depressive disorder (OR=13.20,  $p<0.001$ ) and depressive symptoms ( $\beta=3.87$ ,  $p<0.001$ ).

**Limitations:** The cross-sectional design restrained us to draw any conclusions on causality. The relatively low prevalence of depressive disorder restrained us to adjust for more potential confounders.

**Conclusions:** Type D personality may be a vulnerability factor for depression, irrespective of levels of inflammation or endothelial dysfunction. Future research should examine possible underlying mechanisms.

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## 1. Introduction

Depression is one of the strongest contributors to the global burden of disease (Mathers and Loncar, 2006), leading to the onset of a wide range of cardiovascular diseases (Hare et al., 2014), increasing mortality rates (Cuijpers et al., 2014) and reducing quality

of life (Goldney et al., 2000). The pathogenesis of this disease remains to be elucidated but several biological mechanisms have been proposed to increase the risk for depression such as the vascular depression hypothesis (Krishnan et al., 1997), systemic low-grade inflammation (Valkanova et al., 2013), endothelial dysfunction (Cooper et al., 2011) and chronic dysregulations of the HPA axis (Belvederi Murri et al., 2014). In addition, psychosocial 'vulnerability' factors, such as stressful life events (Paykel, 2003), distorted cognition (Beck, 1991) and Type D (distressed) personality (Pedersen et al., 2006), could also contribute to depression.

The Type D personality construct is characterized by a high score on two stable personality traits; negative affectivity and social inhibition (Denollet, 1993; Denollet and De Potter, 1992). Negative affectivity (NA) refers to the tendency to experience negative emotions such as anger or anxiety across time and situations (Watson and Pennebaker, 1989). Social inhibition (SI) is the tendency to inhibit the expression of emotions and behaviors in social interactions (Asendorpf, 1993).

Previous research suggests that Type D may predict the onset (Pedersen et al., 2006) and persistence (Doyle et al., 2011a) of depressive symptoms in patients with coronary artery disease. Type D personality has also been found to be related to depression in the general population (Michal et al., 2011) and in patients with diabetes (Nefs et al., 2015). It is still unclear why Type D could represent a vulnerability factor for depression. As previously mentioned, biological factors such as low-grade inflammation and endothelial dysfunction may induce depression. Various hypotheses have been proposed as an explanation for the association of inflammation with depression. First, inflammation could induce sickness behavior, which is closely related to or may induce symptoms of depression. A previous review by Dantzer et al. (Dantzer et al., 2008) concluded that pro-inflammatory cytokines are able to cause depressive disorder (cytokine theory of depression), via immune-to-brain communication in which pro-inflammatory cytokines cause feelings of depression via different pathways. Another potential pathway for the association of inflammation with depression refers to the kynurenine hypothesis. This hypothesis postulates that in depression, cortisol-inducible activation of the liver enzyme, tryptophan 2,3-dioxygenase (TDO), shunts metabolism of tryptophan away from serotonin production towards kynurenine production, consequently leading to serotonin deficiency in the brain, and thus contributing to the pathogenesis of depression (Oxenkrug, 2013).

Type D personality has also been related to increased levels of inflammatory biomarkers (Conraads et al., 2006; Denollet et al., 2009; Granville Smith et al., 2015) and reduced endothelial function (Van Craenenbroeck et al., 2009) in patients with cardiovascular disease. Therefore, there is a possibility that low-grade inflammation or endothelial dysfunction could (partly) explain the increased risk of depression associated with Type D personality.

Against this background, the aim of this study was to investigate (A) whether Type D is a vulnerability factor for depression in the Maastricht Study (Schram et al., 2014) and (B) whether Type D is associated with biomarkers of inflammation or endothelial dysfunction. In addition, we examined whether the possible association between Type D and depression is independent of these biomarkers.

## Methods

### Study population

In this study, we used data from the Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously (Schram

et al., 2014). In brief, the study focuses on the etiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus and is characterized by an extensive phenotyping approach, including an extensive module on depression and personality traits. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes status for reasons of efficiency. The present report includes cross-sectional data from the first 712 participants, who completed the baseline survey between November 2010 and March 2012. The examinations of each participant were performed within a time window of three months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Netherlands Health Council under the Dutch "Law for Population Studies" (Permit 131088-105234-PG). All participants gave written informed consent.

### Assessment of Type D personality

Type D personality was measured with the 14-item Type D Scale (DS14) (Denollet, 2005). The DS14 comprises fourteen items that are scored on a five-point rating scale ranging from 0 = "false" to 4 = "true". The scale comprises two subscales, negative affectivity (NA) and social inhibition (SI), containing seven items each. In the present study, a standard cut-off of 10 is used to identify individuals who are high on negative affectivity and/or high on social inhibition (Denollet, 2005). Individuals with a score of  $\geq 10$  on both subscales are considered to have a Type D personality. Both subscales have good test-retest validity and high internal validity with Cronbach's  $\alpha$  of 0.88 and 0.86 for the negative affectivity and social inhibition subscales, respectively (Denollet, 2005). To test the robustness of the Type D model, we classified all participants in four personality categories, to compare the separate and combined effects of high and low trait levels; low negative affectivity/ low inhibition (reference group), low negative affectivity/high inhibition (SI only), high negative affectivity/low inhibition (NA only) and high negative affectivity/high inhibition (Type D).

The DS14 has been validated in previous research, also in primary care patients with type 2 diabetes (Nefs et al., 2012) and healthy controls (Pedersen and Denollet, 2004).

### Assessment of depression

Depressive disorder was assessed by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The MINI is a short diagnostic structured interview, used to assess the presence of minor and major depressive disorder in the preceding two weeks according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Depressive symptoms were assessed with a validated Dutch version of the 9-item Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). The PHQ-9 is a self-administered questionnaire based on the DMS-IV (Association, 1994) criteria for a major depressive disorder. It comprises nine items rated on a four-point scale, ranging from 0 = "not at all" to 3 = "nearly every day". Response options generate a continuous score ranging from 0 (no symptoms) to 27 (all symptoms present nearly every day). The internal consistency of The PHQ-9 is good, with a Cronbach's  $\alpha$  of 0.88 (Lowe et al., 2004).

### Markers of inflammation and endothelial dysfunction

Inflammation and endothelial dysfunction were measured by

use of the plasma biomarkers high sensitivity C-reactive protein (hsCRP), serum amyloid A (SAA), soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF- $\alpha$ ) (inflammation), soluble vascular cell adhesion molecule-1 (sVCAM-1), sICAM-1, E-selectin and Von Willebrand factor (vWF) (endothelial dysfunction), in EDTA plasma with commercially available 4-plex sandwich immunoassay kits (Meso Scale Discovery (MSD), Rockville, MD, US). vWF was determined in citrated plasma with sandwich ELISA (Dako, Glostrup, Denmark) (de Valk-de Roo et al., 1999). Concentrations of vWf were expressed as a percentage of vWf detected in pooled citrated plasma of healthy volunteers. For this study, the intra- and inter-assay coefficients of variation were 3.0% and 4.7% for hsCRP, 2.6% and 7.5% for SAA, 2.5% and 5.3% for sICAM-1, 7.2% and 12.7% for IL-6, 3.1% and 5.6% for IL-8, and 4.3% and 7.5% for TNF- $\alpha$ , 3.5% and 5.9% for sVCAM-1, 2.5% and 5.3% for sICAM-1, 6.4% and 6.0% for E-selectin, and 3.2% and 5.4% for vWF, respectively.

### General characteristics

Partner status, alcohol consumption, total physical activity per week and history of cardiovascular disease were assessed by means of a questionnaire. Smoking behavior was based on self-report of smoking cigarettes, cigars and/or pipe tobacco, and divided into three categories, i.e. non-smoker, former smoker and current smoker. Additionally, lifetime smoking was expressed as pack-years; one pack-year was defined as one packet (=20 cigarettes) per day, smoked over a course of 1 year. Fasting venous blood samples were used to assess glucose levels and HbA<sub>1c</sub>. Medication use was assessed by interview.

To determine type 2 diabetes status, all participants (except those who used insulin) underwent a standardized 7-point oral glucose tolerance test (OGTT) after an overnight fast as previously described. Individuals without type 1 diabetes and on diabetes medication were considered to have T2DM as well (Schram et al., 2014).

### Statistical analyses

Baseline characteristics were compared between individuals with and without Type D personality by use of Independent Samples *T*-test, Mann–Whitney *U* test and Chi-square tests, where appropriate. All variables with a skewed distribution were log-transformed before analyses.

To test the robustness of the Type D model and its association with depression, participants were classified into one of four personality subgroups based on their DS14 scores; a reference group (NA–/SI–), SI only subgroup (NA–/SI+), NA only subgroup (NA+/SI–) and Type D personality subgroup (NA+/SI+). We evaluated whether there were differences in depressive disorder and depressive symptoms across these four personality subgroups using a one-way analysis of variance (ANOVA) with post hoc Bonferroni correction for continuous variables and Chi-square tests for categorical variables.

For reasons of statistical efficiency and to reduce the influence of the biological variability of each measure, an overall standardised sumscore was determined for both inflammation and endothelial dysfunction, according to predefined clusters of conceptually related biomarkers (Heringa et al., 2014). The overall z-scores were calculated as follows: for each individual biomarker, a z-score was calculated according to the formula: (individual value/population mean)/population standard deviation. The resulting individual biomarker z-scores were then averaged into an overall standardised sumscore for both inflammation and endothelial dysfunction using the same formula. The inflammation sumscore

consisted of the biomarkers hsCRP, SAA, sICAM-1, IL-6, IL-8 and TNF- $\alpha$ ; the endothelial dysfunction sumscore consisted of the biomarkers sVCAM-1, sICAM-1, E-selectin and vWF. sICAM-1 was included in both sumscores, as it is expressed by both monocytes and the endothelium (Schram and Stehouwer, 2005). To check whether this influenced the results, we also calculated the overall sumscores for inflammation and endothelial dysfunction without sICAM-1.

Multivariable logistic and linear regression analyses were used to assess the association of Type D personality with depressive disorder (MINI) and depressive symptoms (PHQ-9), biomarkers of inflammation (individual and sumscore) and endothelial dysfunction (individual and sumscore). Multivariable analyses were adjusted for age, sex, type 2 diabetes, prior cardiovascular disease, physical activity, sumscore of inflammation and sumscore of endothelial dysfunction. All statistical tests were two-tailed; a *P*-value < 0.05 was used for all tests to indicate statistical significance.

In posthoc analyses, all items of the PHQ-9 were analyzed across the four personality subgroups, using ANOVA with post hoc Bonferroni correction. Explanatory factor analysis with principal axis factor extraction indicated two latent factors within the PHQ-9, the first factor corresponds with cognitive symptoms of depression (lack of interest, depressed mood, negative feelings about oneself, concentration problems, psychomotor agitation/retardation and suicidal ideation), and the second factor represents somatic symptoms of depression (sleeping problems, fatigability and appetite problems) (Krause et al., 2010). Both factors showed a high internal consistency, with Cronbach's alpha values of respectively 0.88 and 0.70. All statistical analyses were performed using SPSS software, version 19 for Windows.

## Results

### Baseline characteristics

Table 1 shows the study population characteristics according to the presence or absence of Type D personality. The mean age of the total study population at baseline was 59.3 years and 55% were men. In total, 17.3% (*n* = 123) of the participants had Type D personality. People with Type D had significantly higher levels of HbA<sub>1c</sub> and fasting glucose, and were more likely to have type 2 diabetes. In addition, they had higher levels of sICAM-1 and E-selectin. Moreover, people with Type D spent less hours a week on physical activity, compared to people without Type D.

### Type D personality and depression

According to the DS14 scores, 49% (*n* = 349) of the study population were classified in the reference subgroup (neither NA nor SI), 22% (*n* = 153) in the SI-only subgroup, 12% (*n* = 87) in the NA-only subgroup and 17% (*n* = 123) in the Type D subgroup. Of the 123 persons with Type D personality, 22% (*n* = 27) had a diagnosis of depressive disorder and a mean score of 5.9 on the PHQ-9. As depicted in Fig. 1, only 1% of the reference subgroup and the SI-only subgroup had a diagnosis of depressive disorder, as compared to 8% of the NA-only subgroup and 22% of the Type D subgroup. Chi-square tests revealed significant differences on depressive disorder between the Type D subgroup and the NA-only subgroup (*p* = 0.008), Type D subgroup and both the SI-only and reference group (*p* < 0.001) (Fig. 1). In addition, the mean scores on the PHQ-9 were respectively 1.45; 1.95; 4.14 and 5.88 (Fig. 1). ANOVA analyses revealed significant differences on PHQ-9 mean scores between the Type D subgroup and the NA-only subgroup (*p* = 0.001), Type D subgroup and both the SI-only and reference



**Table 1**

General characteristics of the Maastricht Study participants by Type D personality.

	Total population (n=712)	Type D personality		p-Value
		No (n=589)	Yes (n=123)	
Male sex (n)	55% (391)	56% (332)	48% (59)	0.089 <sup>#</sup>
Age, years	59.3 ± 8.5	59.5 ± 8.4	58.3 ± 8.7	0.139 <sup>*</sup>
Having a partner (n)	86% (612)	88% (512)	81% (100)	0.067 <sup>#</sup>
Type 2 diabetes (n)	27% (193)	25% (149)	36% (44)	<b>0.017<sup>*</sup></b>
HbA1c (%)	6.0 ± 0.8	5.9 ± 0.7	6.2 ± 1.0	<b>0.008<sup>**</sup></b>
Fasting glucose level (mmol/L)	6.1 ± 1.5	6.0 ± 1.4	6.4 ± 2.0	<b>0.031<sup>**</sup></b>
Smoking; packyears	13.9 ± 20.8	13.4 ± 19.2	16.2 ± 27.0	0.186 <sup>*</sup>
Never/former/current (%)	32%/53%/15%	32%/53%/15%	32%/52%/16%	0.917 <sup>#</sup>
Alcohol consumption; no/low/high (%)	17%/53%/30%	16%/53%/31%	20%/56%/24%	0.115 <sup>#</sup>
Waist circumference (cm)	97.0 ± 13.7	96.8 ± 13.1	97.8 ± 16.0	0.536 <sup>*</sup>
Total physical activity per week (h/week)	14.2 ± 8.0	14.5 ± 8.2	12.8 ± 7.1	<b>0.040<sup>*</sup></b>
History of cardiovascular disease (n)	17% (118)	17% (95)	20% (23)	0.402 <sup>#</sup>
Depressive disorder (n)	6% (39)	2% (12)	22% (27)	< <b>0.001<sup>#</sup></b>
Depressive symptoms	2.6 ± 3.6	2.0 ± 2.5	5.9 ± 5.7	< <b>0.001<sup>#</sup></b>
<b>Biomarkers of inflammation and endothelial dysfunction</b>				
hsCRP (μg/ml)	1.17 (2.2)	1.14 (2.1)	1.39 (2.4)	0.250 <sup>#</sup>
Median (interquartile range)				
SAA (μg/ml)	2.74 (3.3)	2.69 (3.2)	3.49 (4.5)	0.249 <sup>#</sup>
Median (interquartile range)				
sICAM-1 (ng/ml)	255.2 (62.5)	253.5 (60.3)	263.8 (71.7)	0.097 <sup>*</sup>
IL-6 (pg/ml)	1.40 (1.1)	1.39 (1.1)	1.49 (1.4)	0.278 <sup>#</sup>
Median (interquartile range)				
IL-8 (pg/ml)	3.73 (1.7)	3.71 (1.7)	3.96 (1.9)	0.776 <sup>#</sup>
Median (interquartile range)				
TNF-α (pg/ml)	2.52 (1.0)	2.50 (1.0)	2.68 (1.2)	0.076 <sup>#</sup>
Median (interquartile range)				
sVCAM-1 (ng/ml)	401.7 (98.7)	400.2 (95.1)	408.9 (114.5)	0.435 <sup>*</sup>
E-selectin (ng/ml)	13.2 (7.4)	12.9 (7.1)	14.5 (8.8)	0.066 <sup>*</sup>
vWF (%)	133.4 (46.6)	132.7 (45.3)	136.8 (52.5)	0.424 <sup>*</sup>

Data are presented as mean ± standard deviation unless otherwise indicated.

\*Independent Samples T-Test; #=Chi-square; ^=Mann Whitney-U, \*\*=T-Test, equal variances not assumed.

HbA1c=glycated hemoglobin, hsCRP=high sensitivity C-reactive protein, SAA=serum amyloid A, sICAM-1=soluble intercellular adhesion molecule-1, IL-6=interleukin-6, IL-8=interleukin-8, TNF-α=tumor necrosis factor alpha, sVCAM-1=soluble vascular cell adhesion molecule-1, vWF=Von Willebrand factor.

group ( $p < 0.001$ ).

As shown in Table 1, people with Type D personality were more likely to have a depressive disorder and to suffer from depressive symptoms compared to people without Type D personality.

#### Type D personality and biomarkers of inflammation and endothelial dysfunction

Table 2 shows the association of Type D with biomarkers of inflammation and endothelial dysfunction. Univariate linear regression analyses indicated that Type D personality was significantly associated with the inflammation sumscore ( $\beta$  0.194, 95%-CI 0.00; 0.38,  $p=0.044$ ), also after adjustment for age and sex ( $\beta$  0.228, 95%-CI 0.05; 0.41,  $p=0.014$ ). Univariate linear regression analyses did not indicate a significant association between Type D and the endothelial dysfunction sumscore. However, after adjustment for age and sex, linear regression analyses showed a significant association between Type D and endothelial dysfunction ( $\beta$  0.216, 95%-CI 0.03; 0.40,  $p=0.022$ ) (Table 2). Excluding s-ICAM-1 from the overall sumscores for inflammation and endothelial dysfunction did not change the results (data not shown).

#### Type D personality, depression and biomarkers

As shown in Table 3, Type D was statistically significantly associated with higher levels of depressive disorder (OR 13.67, 95%-CI 6.69; 27.91,  $p < 0.001$ ) and depressive symptoms ( $\beta$  3.95, 95%-CI 3.30; 4.59,  $p < 0.001$ ). After adjustment for age, sex, inflammation and endothelial dysfunction, Type D remained significantly

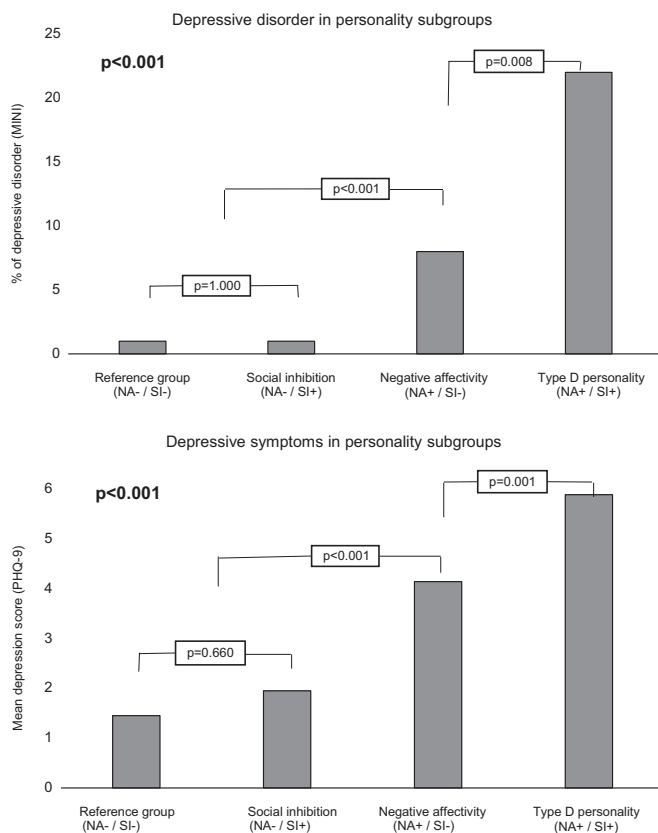
associated with depressive disorder (OR 13.20, 95%-CI 6.38; 27.33,  $p < 0.001$ ) and depressive symptoms ( $\beta$  3.87, 95%-CI 3.22; 4.51,  $p < 0.001$ ) (Table 3). Adjustment for biomarkers of inflammation and endothelial dysfunction did not alter the increased vulnerability to depression associated with Type D, neither did type 2 diabetes and prior cardiovascular disease, nor did physical activity.

#### Post hoc analyses

Type D personality was differentially associated with the nine items of the PHQ-9 (Table 4). Importantly, the Type D subgroup had significant higher levels of anhedonia ( $p=0.005$ ), depressed mood ( $p=0.002$ ), worthlessness ( $p < 0.001$ ), concentration problems ( $p=0.006$ ) and suicide ideation ( $p < 0.001$ ) compared to the NA-only subgroup (Table 4). We also explored whether the association between Type D and depressive symptoms was different for cognitive symptoms versus somatic symptoms, adjusting for inflammation and endothelial dysfunction (online Supplementary Table). The results of the univariate and multivariable linear regression analyses showed that Type D personality was statistically significantly associated with higher levels of both cognitive depressive symptoms (fully adjusted model:  $\beta$  2.61, 95%-CI 2.19; 3.03,  $p < 0.001$ ) and somatic depressive symptoms (fully adjusted model:  $\beta$  1.25, 95%-CI 0.93; 1.56,  $p < 0.001$ ).

#### Discussion

The findings of the current study showed that Type D



**Fig. 1.** Percentage of depressive disorder and mean depression score across personality subgroups.

**Table 2**

Association of Type D personality with individual biomarkers and sumscore of inflammation and endothelial dysfunction.

Dependent variable	Type D personality		
	$\beta$	95% CI	p-Value
Log hsCRP	0.171	−0.02; 0.37	0.086
Log TNF- $\alpha$	0.143	−0.05; 0.33	0.137
Log SAA	0.185	−0.01; 0.38	0.062
sICAM-1	0.153	−0.03; 0.33	0.097
Log IL-6	0.062	−0.14; 0.26	0.541
Log IL-8	0.021	−0.17; 0.21	0.834
<b>Inflammation sumscore</b>	<b>0.194</b>	<b>0.00; 0.38</b>	<b>0.044</b>
<b>Inflammation sumscore*</b>	<b>0.228</b>	<b>0.05; 0.41</b>	<b>0.014</b>
sVCAM-1	0.087	−0.11; 0.28	0.377
sICAM-1	0.153	−0.03; 0.33	0.097
E-selectine	<b>0.209</b>	0.02; 0.40	<b>0.033</b>
vWF	0.086	−0.11; 0.28	0.378
<b>Endothelial dysfunction sumscore</b>	<b>0.171</b>	−0.02; 0.36	<b>0.076</b>
<b>Endothelial dysfunction sumscore*</b>	<b>0.216#</b>	<b>0.03; 0.40</b>	<b>0.022</b>

Data are presented as z-scores.

# A standardized  $\beta$  of 0.216 indicates that the endothelial dysfunction sumscore is 0.216SD higher in individuals with Type D personality compared to individuals without Type D personality.

\* Model is adjusted for age, sex.

personality is a vulnerability factor for depression in the Maastricht Study. Both depressive disorder and depressive symptoms were significantly more prevalent in the Type D subgroup, compared to the NA-only, SI-only and the reference subgroup. Furthermore, when clustering items of the PHQ-9 in cognitive and somatic symptoms of depression, we found that both were

significantly associated with Type D personality. A significant association of Type D personality with biomarkers of inflammation and endothelial dysfunction was found. However, neither inflammation nor endothelial dysfunction altered the association of Type D personality with depression.

Our results are in line with previous research on Type D personality and depression. A longitudinal study of Doyle et al. (2011a) showed that Type D is a vulnerability factor for depression, independently predicting depression and its trajectory over time, confirming previous cross-sectional reports (Doyle et al., 2011b). Also in line with our results are the large effect sizes reported in studies on the association of Type D with depression in patients with diabetes (Nefs et al., 2015). In addition, Hausteiner et al. (2010) demonstrated in a population-based study a 11-fold increased odds of high depressive symptoms for men, and a 7-fold increased odds for women in people with Type D personality.

In our study, we extend these findings by looking beyond the Type D/non-Type D dichotomy to include four different personality groups as a function of high and low NA and SI levels. These analyses showed that higher levels of depression in persons with Type D personality cannot be explained by the NA-trait only. Depressive disorder and depressive symptoms are established to be significantly more prevalent in participants with Type D personality versus participants with only the NA-trait or the SI-trait, in the Maastricht Study. In addition, we observed significant differences between the personality subgroups are presented on individual items of the PHQ-9 questionnaire. All items of the PHQ-9 were significantly different for Type D personality group compared to the SI-only group. Moreover, compared to NA-only subjects, the Type D subgroup had even higher scores on anhedonia, depressed mood, worthlessness, concentration problems and suicide ideation, the cognitive-affective symptoms of depression. This supports the notion that the SI-component, in combination with NA, further increases the risk of depression. This is also in line with previous research among people with coronary artery disease (Bunevicius et al., 2014) showing significant differences in cognitive-affective symptoms of depression between Type D subgroup and NA-only.

Our finding that Type D personality is associated with inflammation is supported by research of Einvik et al. (2011) who found higher levels of hsCRP in people with Type D personality compared to those without. Also a recent study of Hur et al. (2014) showed that Type D personality was independently associated with significant immune activation and increased levels of TNF- $\alpha$  activity. Our results expand these findings, by analyzing multiple inflammatory biomarkers and combining them into predefined clusters of conceptually related biomarkers (Heringa et al., 2014).

Studies on the association of Type D with endothelial dysfunction are scarce. One study reported a reduction of 54% of endothelial progenitor cells in Type D compared with non-Type D persons (Van Craenenbroeck et al., 2009), however, another study reported no association of Type D with endothelial dysfunction (Beutel et al., 2012). To our knowledge, we are the first to examine the association of Type D with endothelial function in a large population-based study, assessing a wide variety of biomarkers, and showing a significant association.

One potential mechanism through which Type D personality might exert a negative influence on depression includes inflammation and/or endothelial dysfunction. We examined this theory, but found no effect of inflammation or endothelial dysfunction in our multivariable analyses. Similar findings were observed in a study of Mommersteeg et al. (2012), who reported that Type D was significantly associated with lower levels of mental health status and increased levels of inflammatory biomarkers in cardiac patients, whereas these biomarkers did not alter the association of Type D with mental health status.

**Table 3**

Association of Type D personality with depression adjusting for inflammation and endothelial dysfunction.

Independent variable	Model	Depressive disorder (MINI)			Depressive symptoms (PHQ-9)		
		OR	95% CI	p-Value	$\beta$	95% CI	p-Value
Type D	1	13.67	6.69; 27.91	< 0.001	3.95	3.30; 4.59	< 0.001
	2	13.83	6.74; 28.38	< 0.001	3.88	3.23; 4.52	< 0.001
	3	13.00	6.30; 26.81	< 0.001	3.75	3.11; 4.39	< 0.001
	4	14.62	6.89; 31.02	< 0.001	3.63	2.99; 4.27	< 0.001
	5	12.93	6.28; 26.61	< 0.001	3.88	3.23; 4.52	< 0.001
	6	13.04	6.32; 26.90	< 0.001	3.82	3.18; 4.45	< 0.001
	7	13.23	6.42; 27.26	< 0.001	3.91	3.26; 4.55	< 0.001
	8	13.20	6.38; 27.33	< 0.001	3.87	3.22; 4.51	< 0.001

Model 1=crude.

Model 2=adjusted for age, sex.

Model 3=adjusted for age, sex, type 2 diabetes.

Model 4=adjusted for age, sex, prior cardiovascular disease.

Model 5=adjusted for age, sex, physical activity.

Model 6=adjusted for age, sex, sumscore of inflammation

Model 7=adjusted for age, sex, sumscore of endothelial dysfunction

Model 8=adjusted for age, sex, sumscore of inflammation and sumscore of endothelial dysfunction.

Apart from increased inflammation or endothelial dysfunction, the association of Type D with depression may be explained by other biological mechanisms. Prolonged disruption of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in high cortisol levels, have been linked to both Type D and depression (Molloy et al., 2008; Otte et al., 2004), as well as increased oxidative stress (Kupper et al., 2009; Smaga et al., 2015). There is also some evidence suggesting that Type D personality may be associated with depression through behavioral pathways. For example, Type D has been associated with an unhealthy lifestyle such as physical inactivity (Hausteiner et al., 2010), which in turn can lead to the development of depression (Dugan et al., 2015). However, in our study, physical activity did not alter the increased vulnerability to depression associated with Type D.

Future studies are needed to explore the possible role of these mechanisms in the association of Type D with depression. The Maastricht Study aims to do this in a longitudinal perspective.

Limitations of the current study must be acknowledged. First, due to the relatively low prevalence of depressive disorder in the study population ( $n=39$ ) we were unable to adjust for more potential confounders, such as socio-economic status. Second, we examined the association of Type D with depression using a cross-sectional design, restraining us to draw any conclusions on causality. Third, we do not have any data on the use of antidepressants or other antidepressant treatment, which could potentially have influenced the results. However, the strengths of our research

should also be highlighted. We used a wide variety of inflammatory and endothelial dysfunction biomarkers, combining them into an overall z-score which reduces the influence of the biological variability of each measure. Furthermore, we used common and validated measures to assess Type D personality and depressive symptoms, as well as depressive disorder.

Our study suggests that Type D personality is an important vulnerability factor for depression, irrespective of biomarkers of inflammation or endothelial dysfunction. Moreover, our research shows that the combination of NA and SI (Type D) may be particularly useful to identify individuals who are at increased risk of depression. Because of the characteristics of Type D personality (inhibition of expression of emotions and behavior in social interaction) it is less likely that these persons will address their emotional state during medical visits. Therefore, the DS14 may aid clinicians in detecting people with Type D personality, who possibly need special clinical attention, since they are at high risk to have depression. In addition, it is apparent that persons with Type D may learn new strategies to reduce their level of distress, for example by means of behavioral interventions, and in turn reduce the likelihood of developing depression (Nyklicek et al., 2013). However, further studies are warranted to examine to which extent these interventions may alter the risk of depression in people with Type D personality.

**Table 4**

Mean scores of individual depressive symptoms (PHQ-9) across personality subgroups.

PHQ-9 item	Reference group	One component of Type D		Type D personality	Type D vs reference, $p$	Type D vs SI only, $p$	Type D vs NA only, $p$
	( $n=349$ ) NA–/SI–	( $n=153$ ) NA–/SI+	( $n=87$ ) NA+/SI–	( $n=123$ ) NA+/SI+			
Loss of interest (a)	0.15 ± 0.39	0.21 ± 0.46	0.51 ± 0.67	0.77 ± 0.83	< 0.001	< 0.001	0.005
Depressed mood (b)	0.05 ± 0.24	0.07 ± 0.31	0.45 ± 0.61	0.68 ± 0.85	< 0.001	< 0.001	0.002
Feeling guilty or worthless (f)	0.05 ± 0.22	0.09 ± 0.28	0.30 ± 0.53	0.59 ± 0.89	< 0.001	< 0.001	< 0.001
Concentration problems (g)	0.13 ± 0.36	0.19 ± 0.47	0.40 ± 0.60	0.65 ± 0.86	< 0.001	< 0.001	0.006
Thoughts about suicide (i)	0.00 ± 0.05	0.01 ± 0.12	0.11 ± 0.41	0.30 ± 0.72	< 0.001	< 0.001	< 0.001
Insomnia/hypersomnia (c)	0.47 ± 0.70	0.68 ± 0.81	0.96 ± 0.85	1.01 ± 0.92	< 0.001	0.005	0.999
Feeling tired or without energy (d)	0.46 ± 0.65	0.54 ± 0.75	0.86 ± 0.75	1.08 ± 0.93	< 0.001	< 0.001	0.227
Change in weight or appetite (e)	0.10 ± 0.32	0.11 ± 0.41	0.35 ± 0.69	0.49 ± 0.81	< 0.001	< 0.001	0.396
Psychomotor agitation/retardation (h)	0.02 ± 0.16	0.03 ± 0.18	0.20 ± 0.58	0.32 ± 0.60	< 0.001	< 0.001	0.128

\* NA=negative affect, SI=social inhibition.

## Conflicts of interest

None.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at: <http://dx.doi.org/10.1016/j.jad.2015.09.028>.

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